

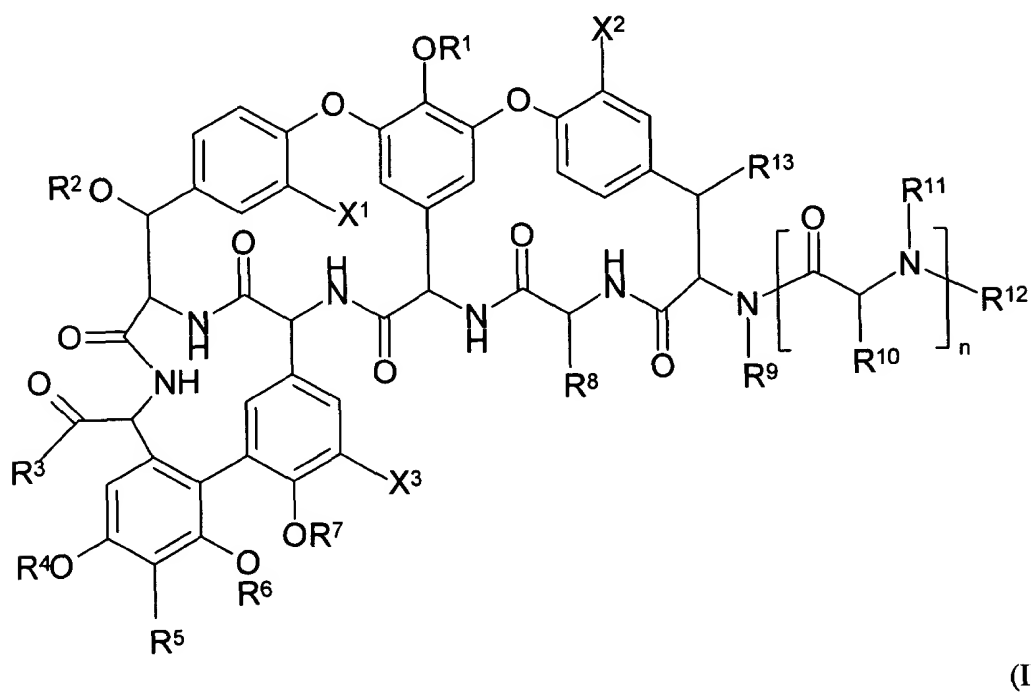
WHAT IS CLAIMED IS:

1. A method for alkylating a glycopeptide that comprises a saccharide-amine comprising:
combining an aldehyde or ketone, a suitable base, and the glycopeptide or a salt thereof, to provide a reaction mixture;
acidifying the reaction mixture; and
combining the reaction mixture with a suitable reducing agent, to provide a glycopeptide that is alkylated at the saccharide-amine.
2. The method of claim 1 wherein the glycopeptide comprises at least one amino group other than the saccharide-amine.
3. The method of claim 2 wherein reductive alkylation at the saccharide-amine is favored over reductive alkylation at the other amino group of the glycopeptide by at least about 10:1.
4. The method of claim 2 wherein reductive alkylation at the saccharide-amine is favored over reductive alkylation at the other amino group of the glycopeptide by at least about 20:1.
5. The method of claim 1 wherein the reductive alkylation is carried out in the presence of a suitable solvent.
6. The method of claim 5 wherein the solvent is a halogenated hydrocarbon, a linear or branched ether, an aromatic hydrocarbon, an alcohol, dimethylsulfoxide, N,N-dimethylformamide, acetonitrile, water, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-

pyrimidone, tetramethyl urea, N,N-dimethylacetamide, diethylformamide, 1-methyl-2-pyrrolidinone, tetramethylenesulfoxide, glycerol, ethyl acetate, isopropyl acetate, N,N-dimethylpropylene urea, or dioxane, or a mixture thereof.

- 5 7. The method of claim 6 wherein the solvent is acetonitrile, water, DMF, or methanol, or mixtures thereof.
8. The method of claim 1 wherein the reaction mixture that is combined with the reducing agent comprises a protic solvent.
9. The method of claim 1 wherein the reductive alkylation is carried out at a temperature in a range of about 0 °C to about 50 °C.
- 10 10. The method of claim 1 wherein the base is a tertiary amine.
11. The method of claim 1 wherein the acid is a carboxylic acid or a mineral acid.
12. The method of claim 1 wherein the acid is trifluoroacetic acid.
13. The method of claim 1 wherein the reducing agent is sodium cyanoborohydride, sodium triacetoxyborohydride, pyridine/borane, sodium borohydride, or zinc
15 borohydride.
14. The method of claim 1 wherein the reducing agent is a hydrogen source and a transition metal catalyst.
15. The method of claim 1 further comprising isolating the alkylated glycopeptide.

16. A method for preparing an alkylated glycopeptide comprising: combining an aldehyde or ketone, a suitable base, and a compound of formula I:



wherein:

R^1 is an amino saccharide group;

5 R^2 is hydrogen or a saccharide group;

R^3 is R^3 is $-OR^c$, $-NR^cR^c$, $-O-R^a-Y-R^b-(Z)_x$, $-NR^c-R^a-Y-R^b-(Z)_x$, $-NR^cR^c$, or $-O-R^e$;

R^4 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, $-C(O)R^d$ and a saccharide group;

10

R^5 is selected from the group consisting of hydrogen, halo, $-\text{CH}(R^c)-\text{NR}^cR^c$, $-\text{CH}(R^c)-\text{NR}^cR^c$, $-\text{CH}(R^c)-\text{NR}^c-R^a-Y-R^b-(Z)_x$, $-\text{CH}(R^c)-R^x$, and $-\text{CH}(R^c)-\text{NR}^c-R^a-\text{C}(=\text{O})-R^x$;

5 R^6 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, $-\text{C}(\text{O})R^d$ and a saccharide group;

R^7 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, and $-\text{C}(\text{O})R^d$;

10 R^8 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

R^9 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

15 R^{10} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic; or R^8 and R^{10} are joined to form $-\text{Ar}^1-\text{O}-\text{Ar}^2-$, where Ar^1 and Ar^2 are independently arylene or heteroarylene;

20 R^{11} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic, or R^{10} and R^{11} are joined, together with the carbon and nitrogen atoms to which they are attached, to form a heterocyclic ring;

25 R^{12} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic,

$-\text{C}(\text{O})\text{R}^{\text{d}}$, $-\text{C}(\text{NH})\text{R}^{\text{d}}$, $-\text{C}(\text{O})\text{NR}^{\text{c}}\text{R}^{\text{c}}$, $-\text{C}(\text{O})\text{OR}^{\text{d}}$, and $-\text{C}(\text{NH})\text{NR}^{\text{c}}\text{R}^{\text{c}}$, or R^{11} and R^{12} are joined, together with the nitrogen atom to which they are attached, to form a heterocyclic ring;

R^{13} is selected from the group consisting of hydrogen or $-\text{OR}^{14}$;

5 R^{14} is selected from hydrogen, $-\text{C}(\text{O})\text{R}^{\text{d}}$ and a saccharide group;

each R^{a} is independently selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene and substituted alkynylene;

10 each R^{b} is independently selected from the group consisting of a covalent bond, alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene and substituted alkynylene;

15 each R^{c} is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic and $-\text{C}(\text{O})\text{R}^{\text{d}}$;

each R^{d} is independently selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

R^{e} is a saccharide group;

20 R^{x} is a nitrogen-linked amino saccharide or a nitrogen-linked heterocycle;

X^1 , X^2 and X^3 are independently selected from hydrogen or chloro;

25 each Y is independently selected from the group consisting of oxygen, sulfur, $-\text{S}-\text{S}-$, $-\text{NR}^{\text{c}}-$, $-\text{S}(\text{O})-$, $-\text{SO}_2-$, $-\text{NR}^{\text{c}}\text{C}(\text{O})-$, $-\text{OSO}_2-$, $-\text{OC}(\text{O})-$, $-\text{NR}^{\text{c}}\text{SO}_2-$, $-\text{C}(\text{O})\text{NR}^{\text{c}}-$, $-\text{C}(\text{O})\text{O}-$, $-\text{SO}_2\text{NR}^{\text{c}}-$, $-\text{SO}_2\text{O}-$, $-\text{P}(\text{O})(\text{OR}^{\text{c}})\text{O}-$, $-\text{P}(\text{O})(\text{OR}^{\text{c}})\text{NR}^{\text{c}}-$, $-\text{OP}(\text{O})(\text{OR}^{\text{c}})\text{O}-$, $-\text{OP}(\text{O})(\text{OR}^{\text{c}})\text{NR}^{\text{c}}-$, $-\text{OC}(\text{O})\text{O}-$, $-\text{NR}^{\text{c}}\text{C}(\text{O})\text{O}-$, $-\text{NR}^{\text{c}}\text{C}(\text{O})\text{NR}^{\text{c}}-$, $-\text{OC}(\text{O})\text{NR}^{\text{c}}-$, $-\text{C}(=\text{O})-$, and $-\text{NR}^{\text{c}}\text{SO}_2\text{NR}^{\text{c}}-$;

each Z is independently selected from hydrogen, aryl, cycloalkyl, cycloalkenyl, heteroaryl and heterocyclic;

n is 0, 1 or 2; and

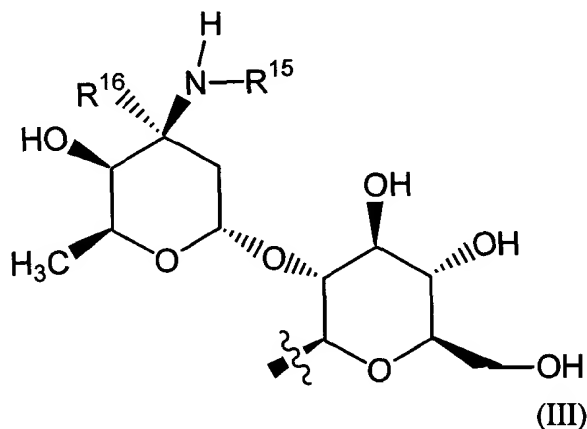
x is 1 or 2;

5 or a stereoisomer or salt thereof; to provide a reaction mixture;

acidifying the reaction mixture; and

combining the reaction mixture with a suitable reducing agent, to provide the corresponding glycopeptide alkylated at the amino group of the amino saccharide.

17. The method of claim 16 wherein R¹ is an amino saccharide of formula (III):



10 wherein R¹⁵ is H; and R¹⁶ is hydrogen or methyl.

18. The method of claim 16 wherein R², R⁴, R⁶, and R⁷ are each hydrogen.

19. The method of claim 16 wherein R³ is -OH.

20. The method of claim 16 wherein R⁵ is hydrogen, -CH₂-NHR^c, -CH₂-NR^cR^e or -CH₂-NH-R^a-Y-R^b-(Z)_x.

21. The method of claim 16 wherein the alkylated glycopeptide is a compound of formula I wherein R¹ is an amino saccharide wherein the saccharide-amine is substituted with -R^a-Y-R^b-(Z)_x, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, or substituted cycloalkenyl.

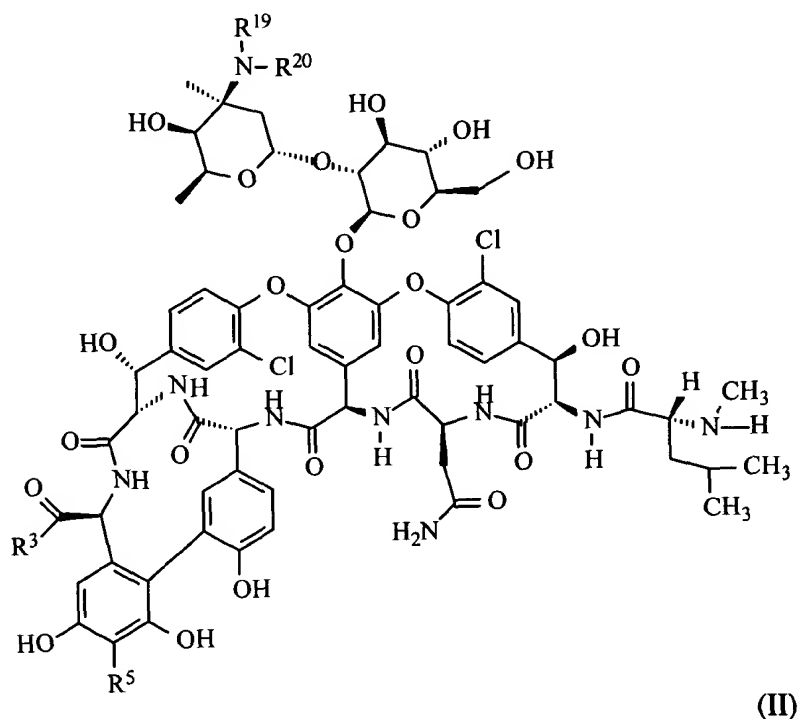
22. The method of claim 16 wherein the alkylated glycopeptide is a compound of formula I wherein R¹ is an amino saccharide wherein the saccharide-amine is substituted with -CH₂CH₂-NH-(CH₂)₉CH₃; -CH₂CH₂CH₂-NH-(CH₂)₈CH₃; -CH₂CH₂CH₂CH₂-NH-(CH₂)₇CH₃; -CH₂CH₂-NHSO₂-(CH₂)₉CH₃; -CH₂CH₂-NHSO₂-(CH₂)₁₁CH₃; -CH₂CH₂-S-(CH₂)₈CH₃; -CH₂CH₂-S-(CH₂)₉CH₃; -CH₂CH₂-S-(CH₂)₁₀CH₃; -CH₂CH₂CH₂-S-(CH₂)₈CH₃; -CH₂CH₂CH₂-S-(CH₂)₉CH₃; -CH₂CH₂CH₂-S-(CH₂)₃-CH=CH-(CH₂)₄CH₃ (*trans*); -CH₂CH₂CH₂CH₂-S-(CH₂)₇CH₃; -CH₂CH₂-S(O)-(CH₂)₉CH₃; -CH₂CH₂-S-(CH₂)₆Ph; -CH₂CH₂-S-(CH₂)₈Ph; -CH₂CH₂CH₂-S-(CH₂)₈Ph; -CH₂CH₂-NH-CH₂-4-(4-Cl-Ph)-Ph; -CH₂CH₂-NH-CH₂-4-[4-(CH₃)₂CHCH₂]-Ph; -CH₂CH₂-NH-CH₂-4-(4-CF₃-Ph)-Ph; -CH₂CH₂-S-CH₂-4-(4-Cl-Ph)-Ph; -CH₂CH₂-S(O)-CH₂-4-(4-Cl-Ph)-Ph; -CH₂CH₂CH₂-S-CH₂-4-(4-Cl-Ph)-Ph; -CH₂CH₂CH₂-S(O)-CH₂-4-(4-Cl-Ph)-Ph; -CH₂CH₂CH₂-S-CH₂-4-[3,4-di-Cl-PhCH₂O]-Ph; -CH₂CH₂-NHSO₂-CH₂-4-[4-(4-Ph)-Ph]-Ph; -CH₂CH₂CH₂-NHSO₂-CH₂-4-(4-Cl-Ph)-Ph; -CH₂CH₂CH₂-NHSO₂-CH₂-4-(Ph-C≡C)-Ph; -CH₂CH₂CH₂-NHSO₂-4-(4-Cl-Ph)-Ph; or -CH₂CH₂CH₂-NHSO₂-4-(naphth-2-yl)-Ph.

23. The method of claim 17 wherein the alkylated glycopeptide is a compound of formula I wherein R¹ is a saccharide group of formula III, wherein R¹⁵ is -R^a-Y-R^b-(Z)_x, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl,

substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl.

24. The method of claim 23 wherein R¹⁵ is -CH₂CH₂-NH-(CH₂)₉CH₃;
-CH₂CH₂CH₂-NH-(CH₂)₈CH₃; -CH₂CH₂CH₂CH₂-NH-(CH₂)₇CH₃;
5 -CH₂CH₂-NHSO₂-(CH₂)₉CH₃; -CH₂CH₂-NHSO₂-(CH₂)₁₁CH₃;
-CH₂CH₂-S-(CH₂)₈CH₃; -CH₂CH₂-S-(CH₂)₉CH₃; -CH₂CH₂-S-(CH₂)₁₀CH₃;
-CH₂CH₂CH₂-S-(CH₂)₈CH₃; -CH₂CH₂CH₂-S-(CH₂)₉CH₃; -CH₂CH₂CH₂-S-(CH₂)₃-
CH=CH-(CH₂)₄CH₃ (*trans*); -CH₂CH₂CH₂CH₂-S-(CH₂)₇CH₃;
-CH₂CH₂-S(O)-(CH₂)₉CH₃; -CH₂CH₂-S-(CH₂)₆Ph; -CH₂CH₂-S-(CH₂)₈Ph;
10 -CH₂CH₂CH₂-S-(CH₂)₈Ph; -CH₂CH₂-NH-CH₂-4-(4-Cl-Ph)-Ph;
-CH₂CH₂-NH-CH₂-4-[4-(CH₃)₂CHCH₂-]-Ph; -CH₂CH₂-NH-CH₂-4-(4-CF₃-Ph)-Ph;
-CH₂CH₂-S-CH₂-4-(4-Cl-Ph)-Ph; -CH₂CH₂-S(O)-CH₂-4-(4-Cl-Ph)-Ph;
-CH₂CH₂CH₂-S-CH₂-4-(4-Cl-Ph)-Ph; -CH₂CH₂CH₂-S(O)-CH₂-4-(4-Cl-Ph)-Ph;
-CH₂CH₂CH₂-S-CH₂-4-[3,4-di-Cl-PhCH₂O-]-Ph; -CH₂CH₂-NHSO₂-CH₂-4-[4-(4-
15 Ph)-Ph]-Ph; -CH₂CH₂CH₂-NHSO₂-CH₂-4-(4-Cl-Ph)-Ph;
-CH₂CH₂CH₂-NHSO₂-CH₂-4-(Ph-C≡C-)-Ph; -CH₂CH₂CH₂-NHSO₂-4-(4-Cl-Ph)-Ph;
or -CH₂CH₂CH₂-NHSO₂-4-(naphth-2-yl)-Ph.

25. A method for preparing an alkylated glycopeptide comprising:
combining an aldehyde or ketone, a suitable base, and a compound of formula II:



wherein:

- R^3 is $-OR^c$, $-NR^cR^c$, $-O-R^a-Y-R^b-(Z)_x$, $-NR^c-R^a-Y-R^b-(Z)_x$, $-NR^cR^c$, or
5 $-O-R^c$;
 R^5 is selected from the group consisting of hydrogen, halo, $-CH(R^c)-NR^cR^c$,
 $-CH(R^c)-NR^cR^c$, and $-CH(R^c)-NR^c-R^a-Y-R^b-(Z)$;
 R^{19} and R^{20} are each hydrogen;
each R^a is independently selected from the group consisting of alkylene,
10 substituted alkylene, alkenylene, substituted alkenylene, alkynylene and substituted
alkynylene;

each R^b is independently selected from the group consisting of a covalent bond, alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene and substituted alkynylene;

5 each R^c is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic and $-C(O)R^d$;

R^e is a saccharide group;

10 each Y is independently selected from the group consisting of oxygen, sulfur, $-S-S-$, $-NR^e-$, $-S(O)-$, $-SO_2-$, $-NR^eC(O)-$, $-OSO_2-$, $-OC(O)-$, $-NR^eSO_2-$, $-C(O)NR^e-$, $-C(O)O-$, $-SO_2NR^e-$, $-SO_2O-$, $-P(O)(OR^e)O-$, $-P(O)(OR^e)NR^e-$, $-OP(O)(OR^e)O-$, $-OP(O)(OR^e)NR^e-$, $-OC(O)O-$, $-NR^eC(O)O-$, $-NR^eC(O)NR^e-$, $-OC(O)NR^e-$ and $-NR^eSO_2NR^e-$;

15 each Z is independently selected from hydrogen, aryl, cycloalkyl, cycloalkenyl, heteroaryl and heterocyclic; and

x is 1 or 2; or a stereoisomer or salt thereof; to provide a reaction mixture; acidifying the reaction mixture; and

20 combining the reaction mixture with a suitable reducing agent, to provide the corresponding alkylated glycopeptide wherein R^{20} is $-R^a-Y-R^b-(Z)_x$, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, or substituted cycloalkenyl.

26. The method of claim 25 wherein R^{20} is $-\text{CH}_2\text{CH}_2-\text{NH}-(\text{CH}_2)_9\text{CH}_3$;
 $-\text{CH}_2\text{CH}_2\text{CH}_2-\text{NH}-(\text{CH}_2)_8\text{CH}_3$; $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-\text{NH}-(\text{CH}_2)_7\text{CH}_3$;
 $-\text{CH}_2\text{CH}_2-\text{NHSO}_2-(\text{CH}_2)_9\text{CH}_3$; $-\text{CH}_2\text{CH}_2-\text{NHSO}_2-(\text{CH}_2)_{11}\text{CH}_3$;
25 $-\text{CH}_2\text{CH}_2-\text{S}-(\text{CH}_2)_8\text{CH}_3$; $-\text{CH}_2\text{CH}_2-\text{S}-(\text{CH}_2)_9\text{CH}_3$; $-\text{CH}_2\text{CH}_2-\text{S}-(\text{CH}_2)_{10}\text{CH}_3$;
 $-\text{CH}_2\text{CH}_2\text{CH}_2-\text{S}-(\text{CH}_2)_8\text{CH}_3$; $-\text{CH}_2\text{CH}_2\text{CH}_2-\text{S}-(\text{CH}_2)_9\text{CH}_3$; $-\text{CH}_2\text{CH}_2\text{CH}_2-\text{S}-(\text{CH}_2)_3-$

- CH=CH-(CH₂)₄CH₃ (*trans*); -CH₂CH₂CH₂CH₂-S-(CH₂)₇CH₃;
 -CH₂CH₂-S(O)-(CH₂)₉CH₃; -CH₂CH₂-S-(CH₂)₆Ph; -CH₂CH₂-S-(CH₂)₈Ph;
 -CH₂CH₂CH₂-S-(CH₂)₈Ph; -CH₂CH₂-NH-CH₂-4-(4-Cl-Ph)-Ph;
 -CH₂CH₂-NH-CH₂-4-[4-(CH₃)₂CHCH₂]-Ph; -CH₂CH₂-NH-CH₂-4-(4-CF₃-Ph)-Ph;
 5 -CH₂CH₂-S-CH₂-4-(4-Cl-Ph)-Ph; -CH₂CH₂-S(O)-CH₂-4-(4-Cl-Ph)-Ph;
 -CH₂CH₂CH₂-S-CH₂-4-(4-Cl-Ph)-Ph; -CH₂CH₂CH₂-S(O)-CH₂-4-(4-Cl-Ph)-Ph;
 -CH₂CH₂CH₂-S-CH₂-4-[3,4-di-Cl-PhCH₂O]-Ph; -CH₂CH₂-NHSO₂-CH₂-4-[4-(4-
 Ph)-Ph]-Ph; -CH₂CH₂CH₂-NHSO₂-CH₂-4-(4-Cl-Ph)-Ph;
 -CH₂CH₂CH₂-NHSO₂-CH₂-4-(Ph-C≡C)-Ph; -CH₂CH₂CH₂-NHSO₂-4-(4-Cl-Ph)-Ph;
 10 or -CH₂CH₂CH₂-NHSO₂-4-(naphth-2-yl)-Ph.

27. The method of claim 1, further comprising preparing a pharmaceutically acceptable salt of the alkylated glycopeptide.

28. The method of claim 1, further comprising, combining a pharmaceutically acceptable carrier with the alkylated glycopeptide to provide a pharmaceutical composition.

29. The method of claim 27, further comprising, combining a pharmaceutically acceptable carrier with the salt, to provide a pharmaceutical composition.